DETAILED ACTION

The amendment filed 1/25/2010 is acknowledged. Claims 1, 2, 4, 9, 12 and 15-30 are pending and examined on the merits.

Claim Objections/ Rejections Withdrawn:

Claim Objections

The objection to claims 18 and 19 for depending from canceled claim 3 is withdrawn in view of the amendment to the claims.

The rejection of claims 1, 2, 4, 15-23, 25 and 30 under 35 U.S.C. 103(a) as being unpatentable over Obiakor (Obiakor, H. et al., Analytical Biochemistry, 306: 55-62, 2002, June), in view of Walton (Walton, L., J., et al., Atherosclerosis, 135: 65-71, 1997) is withdrawn in view of the amendment to the claims requiring the step of obtaining a polynucleotide encoding an antibody heavy chain and a polynucleotide encoding an antibody light chain, wherein the antibody is specific for an antigen of the lesional tissue.

Claim Rejections Maintained and New Grounds of Rejection:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4, 9, 12, 15-22, and 28-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods wherein the lesional tissue is cancer tissue, an inflammatory disease lesion, a lesion generated by an infectious disease pathogen, an autoimmune disease lesion, or an artificially prepared lesion, does not reasonably provide enablement for methods wherein the lesional tissue is an arteriosclerotic lesion. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation would be required to practice the full scope of the claimed inventions are: 1) quantity of experimentation necessary; 2) the amount of direction or guidance presented in the specification; 3) the presence or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the relative skill of those in the art; 7) the predictability or unpredictability of the art; and 8) the breadth of the claims. See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

The claims are drawn to methods comprising isolating a polynucleotide from a single B cell from any lesional tissue, wherein the polynucleotide encodes an antibody that is specific for an antigen of the lesional tissue. Among the tissues contemplated is an arteriosclerotic lesion.

The specification provides an example of isolating B cells from a cancerous lesion, but no example of isolating a B cell from an arteriosclerotic lesion, wherein the B cell expresses an antibody that binds to an antigen of the arteriosclerotic lesion. Walton (of record; Walton, L., J., et al., Atherosclerosis, 135: 65-71, 1997) provides data that shows that arteriosclerotic lesions contain B cell infiltrations, but that these B cells are polyclonal, and therefore are not likely to be B cells that are present due to an autoimmune process. Thus, neither the prior art nor the

specification provides data showing that arteriosclerotic lesions contain B cells that express an antibody that binds to an arteriosclerotic lesion.

In view of the breadth of the claims, where the claims encompass arteriosclerotic lesions, and in view of the limited disclosure where the method is directed to isolation of B cells expressing antibodies that bind to cancerous antigens, and in view of the teachings of Walton that arteriosclerotic lesions do not in general appear to contain arteriosclerotic-specific antigen directed B cells, it would require further and undue experimentation on the part of the skilled worker to practice the full scope of the claimed methods. The further experimentation would be undue because neither the specification nor the prior art has established that arteriosclerotic lesions contain B cells expressing antibodies that bind to arteriosclerotic-lesion specific antigens.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 4, 15-21, 27 and 30 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Obiakor (Obiakor, H. et al., Analytical Biochemistry, 306: 55-62, 2002, June; of record) in view of Kotlan (Kotlan, B. et al., Immunology Letters, 65: 143-151, 1999; cited in IDS) for the reasons of record.

Applicants state that the examiner's rationale for combining Obiakor with Kotlan is based on an incorrect understanding of the Kotlan reference, because Kotlan is directed to investigating the immunobloulin (Ig) repertoire of B lymphocytes infiltrating a breast medullary carcinoma of a single cell suspension as opposed to a solution in which just one single cell is suspended; whereas it is applicants' belief that Kotlan intended single cell suspension to mean a mixture of many cells in the suspension were not attached to each other. Applicants state that the rationale provided for combining the teachings of Obiakor with the teachings of Kotlan is that both Obiakor and Kotlan teach methods from the same field of endeavor: isolation and determination of polynucleotide sequences of immunoglobulins from single B cells. Applicants state that Kotlan's purpose, understanding the entire repertoire of Igs present in a breast medullary cancer,

was much more efficiently achieved by the straightforward batch-preparation technique utilized by Kotlan than it would have been by a technique such as Obiakor's that requires sequential isolation and analysis of single cells.

Applicants' arguments are not found persuasive because in the previous Office action, the rationale for combining the teachings of Obiakor with Kotlan was not that Kotlan taught making a suspension of single B cells, but that Kotlan taught B cells are present in lesional tissues such as breast cancers and that nucleotides encoding antibodies may be isolated from these B cells. There is no need for Kotlan to teach making a suspension with a single B cell because Obiakor teaches the use of laser microdissection to isolate a single B cell for the purpose of isolation and determination of polynucleotide sequences of immunoglobulins from a single cell.

Applicants state that the Office action provides only a conclusory statement regarding a reason one of ordinary skill would wish to modify Obiakor with Kotlan; and that stating that a reason exists instead of saying what the reason exists is wholly inadequate to support a prima facie case of obviousness.

Applicants' arguments are not found persuasive because when the statement was made that "there is reason [sic] to isolate and determine the polynucleotide sequences encoding antibodies in B cells infiltrating cancer tissues", the Office action was summarizing the teachings of Kotlan. Kotlan teaches that V genes from B lymphocytes are now readily cloned and sequenced in bacteria as Fab or scFv fragments, and that Zhang et al succeeded in making human anti-tumor single-chain antibodies from melanoma TIL-B cells by PCR cloning (page 144, left to right columns, bridging paragraph). Therefore, Kotlan teaches that B lymphocytes infiltrating tumor tissues are a source of anti-tumor antibodies. Although the experiments of Kotlan are not

directed to making anti-tumor antibodies, Kotlan does teach that in the prior art the concept of using TIL-B cells as a source of anti-tumor immunoglobulin sequences is known. Obiakor teaches that when DNA is derived from multiple germinal center B cells instead of single cells, a PCR artifact-hybrid gene is formed (see page 55, right column). Therefore, Obiakor provides a reason for isolating a single B cell as a source of immunoglobulin DNA.

Claims 9, 12, 28 and 29 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Obiakor (Obiakor, H. et al., Analytical Biochemistry, 306: 55-62, 2002, June; of record) in view of Zhang (Zhang, H. et al., Cancer Research, 55: 3584-3591, 1995; cited in IDS) for the reasons of record.

Applicants state that there is no motivation to combine Obiakor and Zhang because Zhang is concerned with identifying a subset of B cells that produce anti-tumor immunoglobulins, and Obiakor is concerned with examining a cross-section of all B cells present in a tissue. Applicants state that the Office action seems to assume that every B cell present in a tumor will bind to a tumor-specific antigen, and that there is no evidence to support this assumption. Applicants state that it is possible that a large majority of B cells in a lesional tissue may not bind tumor antigens, and that Zhang's method which involves identifying tumor-antigen-specific B cells.

Applicants' arguments have been carefully considered, but fail to persuade. Zhang teaches that the method used is based on the hypothesis that tumor-reactive B cells are enriched in tumors (see page 3585, left column). Also, Zhang's method involves, ultimately isolating single cells by limiting dilution and then constructing scFv. Thus, before the scFv are

constructed, Zhang's method has not identified which well is associated with an anti-tumor immunoglobulin. Since Obiakor's method involves sampling a cross-section of lesional tissue to isolate single cells, and since it has been established in the prior art that tumor reactive B cells exist in tumor lesions, the benefit of Obiakor's method is that the chance of producing a PCR artifact-hybrid gene is decreased. Therefore, the rejection is maintained for the reasons of record.

Claims 1, 2, 4, 15-21, 23-26 and 30 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Obiakor (Obiakor, H. et al., Analytical Biochemistry, 306: 55-62, 2002, June), in view of Mallison (Mallison, S. M. et al., Infection and Immunity, 59(11): 4019-4025, 1991).

Applicants state that there is no teaching or suggestion whatsoever in Mallison regarding the need or desirability to isolate a single B cell from the lesional tissue and to obtain a polynucleotide encoding an antibody heavy chain and a polynucleotide light chain of the isolated B cells. Applicant states that Mallison already knows the antigen, horseradish peroxidase, and thus there is no need to identify the antigen that the antibody secreted by the B cells bind or to identify the immunoglobulin sequences.

Applicants' arguments have been carefully considered, but fail to persuade. Mallison teaches that the B lymphocytes in the chronically inflamed gingivitis lesions are locally specific (see page 4024). Therefore, Mallison provides motivation to isolate B cells and identify the polynucleotides encoding antibodies that bind to antigen or antigens that play a role in the pathogenesis of peiodontal disease. The rejection is maintained for the reasons of record.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne Holleran, whose telephone number is (571) 272-0833. The examiner can normally be reached on Monday through Friday from 9:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached on (571) 272-0832. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Official Fax number for Group 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Anne L. Holleran
Patent Examiner
April 20, 2010

/Alana M. Harris, Ph.D./

Primary Examiner, Art Unit 1643